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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,519	05/01/2002	Audrey Goddard	P3230R1C001-168	8149

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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,519	EATON ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-5

DETAILED ACTION

1. Claim 6 has been canceled.

Claim 1 has been amended.

2. Claims 1-5 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Inventorship

4. The request for the deletion of inventors Eaton, Filvaroff, Gerritsen, and Watanabe is approved and the inventors have been deleted.

Rejections Withdrawn

5. The rejection of claims 1 and 6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

Response to Arguments

6. The rejection of claims 1-5 under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility is maintained.

The response filed 5/2/05 has been carefully considered, but is deemed not to be persuasive. The response argues that the identification of the differential expression of the PRO polypeptide-encoding nucleic acid in melanoma compared to normal skin tissue and that it is well established that the change in the level of mRNA encoding a particular protein generally leads to a change in the corresponding protein and given that the PRO1864 polypeptide is increased in melanoma compared to normal skin it is likely that the pro polypeptide is differentially expressed and can be used as a diagnostic tool (see page 12-13 of response) and in the majority of cases, gene expression correlates with levels of protein expression and submits the declaration of Dr. Grimaldi (Exhibit 1 and 2) and the submitted declaration of Dr. Polakis (Exhibit 3) states that it remains a central dogma that increased levels of mRNA are predictive of increased levels of protein and cites Alberts, Lewin and Zhingang et al for support (see pages 12-16 of the response). In response to this argument, the declarations and art cited by Applicant have been carefully considered but are deemed not to be persuasive. The Grimaldi declarations have been considered but only states that Example 18 showed mRNA expression and the declaration does not state that the protein was expressed it only states that the peptide and antibodies to the peptide can be useful for

diagnostics. The other Grimaldi declaration states that it is unlikely that one identifies increase or decrease mRNA without the associated protein and in a rare case that the protein does not correlate with mRNA this would still provide crucial information for the clinician. In response to this the examiner cited numerous art that did show mRNA does not correlate with protein and as such the instance is not so rare as indicated in the declaration. The Polakis declaration states that in 80% of the observations they have found that increases in the levels of a particular mRNA correlates with changes in the level of protein expressed from that mRNA in human tumor cells. In response to this argument, the examiner again cited art in the 112 first rejection that supports that mRNA over-expression does not correlate with protein over-expression. Further, while the declaration may show a correlation between mRNA and protein over-expression in some cases, no evidence has been submitted that it is the norm rather than the exception that protein levels parallel gene expression in cancer cells. The response cites Alberts, Lewin and Zhigang for support fro mRNA correlates with protein (see page 16-17 of response). In response to this argument, Alberts and Lewin actually support the unpredictability in that they teach controls and at several levels these controls can have an effect on expression of the protein. The art of Zhigang et al does show protein expression, however, the experiments were carried out to demonstrate this and as such Zhigang et al support that one needs to actually determine the expression of the protein in order to be sure of expression. As evidenced by Gokman-Polar et al (Cancer Research, 2001, 61:1375-1381), the absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar

et al (Cancer Research, 2001, 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level" (see abstract). Gokman-Polar et al show in figures 6 and 7 that there is no increase in mRNA expression for any of the isoenzymes, while the protein is significantly overexpressed as shown by figures 4 and 5.

The response states that Haynes actually support the assertion of mRNA correlates with protein and cites Gygi to provide that correlation is high for highly expressed mRNA (see page 18-19 of response). In response to this argument, Gygi actually states that We found that correlation between mRNA and protein levels were insufficient to predict protein expression and states that those that were correlated suggested an importance of posttranslational mechanisms controlling gene expression and that simple deduction from mRNA analysis is insufficient (see abstract and page 1727).

The response states that the general findings of Hu are not surprising and the strongest known relationship to disease is measured by the greater change in expression level and Hu's methodology yields results that prove little or no information regarding the biological significance of genes with less than 5 fold expression change (see page 20-22 of response). In response to this, the argument does not present any evidence that under 5 fold would be useful for diagnosis as asserted because the PRO1864 is only overexpressed at 2 fold.

Therefore, in view of the art cited by the examiner in the 112 first rejection and as evidenced by Gokman-Polar et al above it is not necessarily the norm that gene expression, or even transcription, parallels protein expression. Thus, in view of the totality of evidence, the skilled artisan would not assume that gene expression necessarily parallels or is predictive of protein expression, but would perform the experiment to verify it.

Finally, Applicant refers to the Ashkenazi declaration (Exhibit 12), which argues that assuming arguendo that there is no correlation between gene expression and decreased protein expression for PRO1864, a polypeptide encoded by a gene that is under or over-expressed in cancer would still have utility and identification of both gene and protein expression provide a more accurate tumor classification and hence better determination of suitable therapy. This has been fully considered but is not found to be sufficient to withdraw this rejection, since there is no indication that PRO1864 protein levels increase or stay the same. Further research would be required to determine PRO1864 protein levels in cancers showing gene amplification of PRO1864. Therefore, the asserted utility is not substantial as the real-world use has not been established and also is not specific because Applicant has not provided any objective evidence correlating the expression of the PRO1864 polypeptide with any particular disease state (e.g., kidney tumor). As the utility guideline materials note at page 5-6 (See: Federal Register: December 21, 1999 (volume 64, Number 244), revised guidelines for Utility), "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be

diagnosed". Thus, the proposed use of the PRO1864 protein are simply starting points for further research and investigation into potential practical uses of the protein and antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "[i]t is not a reward for the search, but compensation for its successful conclusion."

Therefore, the rejection under 35 U.S.C 101 is maintained.

7. The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph is maintained. Specifically, since the claimed invention is not supported by a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention is maintained for the reasons above.

8. The rejection of claims 1-5, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 5/2/05 has been carefully considered but is deemed not to be persuasive. The response states that addressed above is Lewin that the majority of regulation happens at transcription and this reference as well as others above and the declarations of Polakis and Grimaldi above provide support for correlation of mRNA and protein. In response to this argument the references have been addressed and because the examiner has supplied (and countered the references supplied and declarations supplied) evidence for unpredictability in the art, the evidence presented is for unpredictability in the art.

The response states that Pennica says nothing about the lack of correlation. In response to this argument, again Pennica demonstrates that each gene amplification and correlation to protein overexpression needs to be determined by a case by case basis because even Pennica's three gene expression do not correlate and one skill in the art would not disregard the data in a paper just because it did not confirm ones theory.

Thus, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the protein's expression including the correlation to a diseased state, one of skill in the art would be unable to predictably use the polypeptides in any diagnostic setting without undue experimentation.

In view of the lack of guidance, lack of examples, and lack of predictability in the art and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 571-273-8300.

Larry R. Helms

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER